REMARKS

This Amendment, filed in reply to the Office Action dated September 11, 2008, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested. Claim 1 is amended herewith to even further clarify Applicants' claimed invention. Claim 4 is amended herewith solely to improve clarity. No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Claim to Priority

Applicants note that a certified copy of Chinese Application No. 02156785.9, filed December 18, 2002, has been submitted, and the claim to foreign priority is correctly listed on the Declaration filed June 20, 2005. Accordingly, Applicants respectfully request that the Examiner formally acknowledge Applicants' claim to foreign priority, and receipt of the priority document.

Elections/Restrictions

On page 2 of the Office Action, the Examiner asserts that Applicants' traversal arguments in response to the Restriction Requirement are unpersuasive. Specifically, the Examiner contends that a showing of a lack of unity of invention is not required to maintain the Restriction because the polynucleotides recited in Claims 1-7 and 9-12 are "subject to restriction in domestic applications." The Examiner concludes that restriction to a single nucleotide sequence is proper on this basis.

Applicants respectfully disagree, and request reconsideration of the Requirement in view of the following remarks.

First, Applicants respectfully point out that Restriction to a single amino acid or nucleotide sequence on the basis that searching additional sequences would constitute an undue burden is **not** the proper legal standard for Restriction of nucleotide and amino acid sequences in National Stage filings of International Applications under 35 U.S.C. § 371. Rather, to support Restriction of amino acid or nucleotide sequences in National Stage filings of International Applications, the Examiner must find a lack of unity of invention between the sequences, *i.e.*, a showing that the sequences lack a special technical feature which makes a contribution over the prior art. An allegation of "undue search burden" is insufficient grounds to support a lack of unity of invention, and thus Restriction. Because the Restriction is made final on the basis that searching the sequences would constitute an undue burden, and because Applicants' arguments that the sequences possess unity of invention have not been considered because the sequences are allegedly "subject to restriction in domestic applications," the Examiner's legal position is in clear error.

For the Examiner's edification, the "Examination Guidelines" in the addendum published February 2, 2007, state that:

> For National applications filed under 35 U.S.C. 111(a), polynucleotide inventions will be considered for restriction, rejoinder and examination practice in accordance with the standards set forth in MPEP Chapter 800 (except for MPEP 803.04 which is superceded by this Notice). Claims to polynucleotide molecules will be considered for independence, relatedness, distinction and burden as for claims to any other type of molecule.
>
> For International applications **and national stage filings of international applications** under 35 U.S.C. 371, **unity of invention determination will be made** in view of PCT Rule 13.2, 37 CFR 1.475 and Chapter 10 of the ISPE Guidelines. Unity of invention will exist

> when the polynucleotide molecules, as claimed, share a general inventive concept, i.e., share a technical feature which makes a contribution over the prior art. [Emphasis added.]

Accordingly, the reasons supporting Restriction set forth in the Office Action mailed May 23, 2008, and the Examiner's assertion that the Restriction is properly final on the basis that the instant sequences are "subject to restriction in domestic applications," lack proper legal basis. The Restriction is improper, and should be withdrawn.

Withdrawal of the Restriction is respectfully requested.

Claims 1-7 and 9-12 are Patentable Under 35 U.S.C. § 103

On page 4 of the Office Action, Claims 1-7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozal *et al.* (U.S. Patent No. 5,631,128), Pavlakis *et al.* (U.S. Patent No. 5,965,726) and Kraus *et al.* (U.S. Patent No. 5,958,768), and further in view of Fire *et al.* (U.S. Patent No. 6,506,559) and Schwarz *et al.* (*Cell*, Vol. 115, pages 199-208, 2003).

In making the rejection, the Examiner asserts that Kozal *et al.* and Pavlakis *et al.* each disclose single stranded oligonucleotides "that specifically target the nucleic acid sequence encoding gag of HIV, including a 29 nucleotide fragment of SEQ ID NO: 3." The Examiner cites to Kraus *et al.* to support the contention that the use of nucleic acid constructs comprising DNA or RNA, and encoding antisense and ribozymes for specifically targeting and inhibiting the expression of HIV, was known in the art. However, the Examiner acknowledges that neither Kozal *et al.*, Pavlakis *et al.*, or Kraus *et al.* disclose an siRNA having 19-28 nucleotides of SEQ ID NO: 3, or a molecule containing its complement in a hairpin conformation, or siRNAs comprising uracil dinucleotide overhangs at either the 5' or 3' termini.

In an attempt to rectify the deficiencies of Kozal *et al.*, Pavlakis *et al.*, and Kraus *et al.*, the Examiner cites to Fire *et al.*, who allegedly disclose that siRNA molecules may be two-separate complementary strands, or a self-complementary strand comprising a non-complementary loop joining the self-complementary regions to form a hairpin.

The Examiner relies upon Schwarz *et al.* for the disclosure that siRNA molecules may be between 19 and 28 nucleotides, and that dinucleotide overhangs may be appended to the 5' or 3' termini of the siRNA molecules, such as uracil dinucleotide overhangs.

The Examiner takes the position that one of ordinary skill in the art would readily have designed siRNA molecules having between 19-28 nucleotides of SEQ ID NO: 3 to inhibit HIV, because "the target region of HIV encoded by SEQ ID NO: 3 was well known in the art ... and was well known as a target region of HIV that was susceptible to antisense or probe binding, as taught previously by Kozal and Pavlakis." The Examiner also contends that one of ordinary skill in the art would reasonably have expected that siRNAs having 19-28 nucleotides of SEQ ID NO: 3 would successfully target and inhibit expression of HIV "because this region was well known as an important region (e.g. gag-pol) for viral replication, and this region was well known as an accessible target region for probe or antisense binding."

Applicants disagree with the rejection, and traverse, respectfully. For the reasons set forth below, the rejection relies entirely on impermissible hindsight reconstruction. The cited references, taken alone, or in combination, do not reasonably suggest using instant SEQ ID NO: 3, or a 18-29 nucleotide fragment thereof, as an siRNA, much less using double-stranded molecules with or without hairpins, or adding uracil dinucleotide overhangs. Further, a *prima facie* case of obviousness has not been established, because one of ordinary skill in the art would

not possess a reasonable expectation of success that such a molecule would function as an siRNA, as is required by law to maintain such a rejection.

First, Applicants note that Kozal *et al.* and Pavlakis *et al.* are relied upon to support the contention that SEQ ID NO: 3 was well known in the art as a target region of HIV susceptible to antisense or probe binding. However, Applicants respectfully disagree that those of ordinary skill in the art would have understood such from Kozal *et al.* and Pavlakis *et al.* In Kozal *et al.*, an oligonucleotide primer (*i.e.*, SK 19; SEQ ID NO: 3 in Kozal *et al.*) is used as a labeled oligonucleotide probe for hybridization with a PCR product to detect the presence of a specific PCR product (*i.e.*, hybridization to a **DNA template**). Thus, contrary to that asserted in the rejection, Kozal *et al.* neither disclose or even reasonably suggest that the sequence represented by SEQ ID NO: 3 in HIV **RNA** is susceptible to antisense or probe binding, because the probe used by Kozal *et al.* was only tested for binding to a PCR product (*i.e.*, **DNA**). Accordingly, Kozal *et al.* say nothing as to whether the region of HIV **RNA** represented by SEQ ID NO: 3 is susceptible to probe or antisense oligonucleotide binding, much less that this region would be suitable for siRNA-mediated inhibition of gene expression.

Similarly, regarding Pavlakis *et al.*, the Examiner refers to a disclosed SEQ ID NO. which contains instant SEQ ID NO: 3, and contends that one of ordinary skill in the art would understand from Pavlakis *et al.* that this sequence in HIV **RNA** is susceptible to antisense oligonucleotide or probe binding. However, for the same reasons, Applicants disagree. Applicants respectfully point out that Pavlakis *et al.* is directed to the substitution of HIV nucleotides within viral RNA so as to remove sequence motifs which reduce the half-life of the RNA. At no point do Pavlakis *et al.* demonstrate or even suggest accessibility of antisense or probe binding to the region of HIV **RNA** represented by SEQ ID NO: 3. Rather, Pavlakis *et al.*

engineer **DNA** expression vectors to produce modified RNA transcripts lacking these instability elements. Indeed, and the sequence disclosed by Pavlakis *et al.* which contains instant SEQ ID NO: 3 is merely an oligonucleotide used to introduce nucleotide substitutions into a **DNA** plasmid containing the HIV *gag* gene. Thus, like Kozal *et al.,* Pavlakis *et al.* say nothing as to whether the region of HIV **RNA** represented by SEQ ID NO: 3 is susceptible to probe or antisense oligonucleotide binding, much less that this region would be suitable for siRNA-mediated inhibition of gene expression.

In addition, Applicants note that Kraus *et al.* merely provide a generic disclosure that ribozymes may be useful for cleaving HIV RNA. Kraus *et al.*, however, do not even contemplate that the specific region of the *gag* gene represented by instant SEQ ID NO: 3 could be used for such a purpose. Accordingly, the rejection is deficient at least because Kozal *et al.*, Pavlakis *et al.*, and Kraus *et al.*, taken alone or in combination, provide no guidance whatsoever to one of ordinary skill in the art that a viral **RNA**, having a sequence corresponding to instant SEQ ID NO: 3, would be accessible to antisense or probe binding, much less that targeting this region would be expected to reduce gene expression. Fire *et al.* and Schwarz *et al.* provide no further motivation or guidance to select this region vis-à-vis any other nucleotide sequence in the HIV genome, as they pertain to generic methods for siRNA inhibition.

Second, as discussed above, Kozal *et al.* and Pavlakis *et al.* merely disclose that oligonucleotides having the sequence of instant SEQ ID NO: 3 can hybridize to a **DNA** template *in vitro*. As would be readily appreciated by one of ordinary skill in the art, the technical considerations for designing oligonucleotides for effective hybridization (such as for PCR, southern blotting, or primer-based mutagenesis) are completely different to those for designing siRNAs which effectively inhibit gene expression through the RISC complex. Given the high

level of skill in the genetic arts, one of ordinary skill in the art would clearly not expect from reading Kozal *et al.*, Pavlakis *et al.*, and Kraus *et al.*, that instant SEQ ID NO: 3 would be effective as an siRNA simply because the complementary region of the *gag* gene, **when converted to DNA**, can be hybridized with a complementary oligonucleotide primer. Indeed, in column 3, lines 27-34 of Fire *et al.*, Fire *et al.* clearly distinguish siRNA over antisense RNA mechanistically. Specifically, Fire *et al.* state that "we disclose that in the model organism *C. elegans*, the present invention is at least 100-fold more effective than an equivalent antisense approach (i.e., dsRNA is at least 100-fold more effective than the injection of purified antisense RNA [i.e., single stranded RNA] in reducing gene expression). These comparisons also demonstrate that inhibition by double-stranded RNA must occur by a mechanism **distinct** from antisense interference." (Emphasis added.) Accordingly, Fire *et al.*, make clear that antisense RNA inhibition works through a distinct mechanism to siRNA. Therefore, even assuming *arguendo* that one of ordinary skill in the art were to understand from Kozal *et al.* and Pavlakis *et al.* that the specific region of the *gag* RNA represented by instant SEQ ID NO: 3 would be susceptible to antisense binding, which they would not for the reasons set forth above, they would nevertheless realize from Fire *et al.* that antisense inhibition occurs through a mechanism distinct to siRNA inhibition, and thus that suitability as an antisense target says nothing as to whether instant SEQ ID NO: 3 would be effective as an siRNA. For this reason, one of ordinary skill in the art would have possessed no motivation to modify SEQ ID NO: 3 to make it double-stranded, as currently claimed, much less to make it between 18-29 nucleotides in length (as suggested solely for siRNAs by Schwarz *et al.*), to include a hairpin, or to add uracil dinucleotide overhangs (which are also suggested solely for siRNAs), because such modifications are irrelevant to antisense oligonucleotides.

In addition to the above arguments, Applicants submit that one of ordinary skill in the art would not have possessed a reasonable expectation of success in using SEQ ID NO: 3 as an siRNA, given the high degree of unpredictability in the art at the time of filing concerning which nucleotide structures exhibit siRNA activity. Fire *et al.* make clear that inhibition through siRNAs is mechanistically distinct to inhibition through antisense oligonucleotides, and therefore, one of ordinary skill in the art would not design an siRNA with a reasonable expectation of success on the basis that the target sequence, when reverse transcribed to **DNA**, merely can be hybridized with an oligonucleotide DNA primer. Indeed, such says nothing even with regard to the suitability as a target for antisense inhibition of gene expression, much less suitability as a target for siRNA-mediated inhibition. Given such unpredictability, it would not even have been "obvious to try" using SEQ ID NO: 3 as an siRNA, because as was held in *KSR International Co. v. Teleflex Inc.*, obviousness predicated on an "obvious to try" rationale requires that there be a finite number of **identified**, **predictable** solutions. SEQ ID NO: 3 was neither identified, nor predictable, as a functioning siRNA.

For the foregoing reasons, Applicants respectfully submit that the cited references do not render obvious the presently claimed invention.

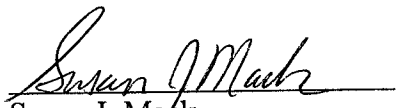
Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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